(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 December 2004 (23.12.2004)

PCT

(10) International Publication Number
WO 2004/111038 A1

(51) International Patent Classification[7]: C07D 401/14, A61K 31/497, A61P 3/04, 25/00, 37/00, 09/00, 05/00, 11/00 // 01/00, C07D 401/14, 241/24, 211/06

(21) International Application Number: PCT/SE2004/000967

(22) International Filing Date: 16 June 2004 (16.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0314049.8 18 June 2003 (18.06.2003) GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 5,6-BIS (4-CHLOROPHENYL)-N-PIPERIDIN1-YL-3-(PIPERIDIN-1-YL-CARBONYL)PYRAZINE-2-CARBOXAMIDE

(57) Abstract: The present invention relates to 5,6-bis(4-chlorophenyl)-N-piperidin1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide, to processes for preparing this compound, to its use in the treatment of obesity, psychiatric and neurological disorders, to methods for its therapeutic use and to pharmaceutical compositions containing it. The compound is a cannabinoid receptor 1 (CB1) modulator.

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5,6-bis(4-chlorophenyl)-N-piperidin1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide.

Field of invention

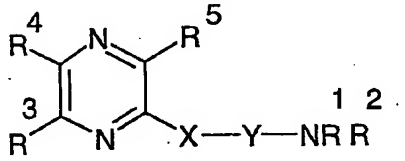
The present invention relates to a pyrazine compound, to processes for preparing this compound, to its use in the treatment of obesity, psychiatric and neurological disorders, to methods for its therapeutic use and to pharmaceutical compositions containing it.

Background of the invention

It is known that certain CB_1 modulators (known as antagonists or inverse agonists) are useful in the treatment of obesity, psychiatric and neurological disorders (WO01/70700 and EP 656354). However, there is a need for CB_1 modulators with improved physicochemical properties and/or DMPK properties and/or pharmacodynamic properties.

Pyrazinecarboxamides are reported to possess antithrombotic properties (WO 92/ 02513). The compounds disclosed in this document are disclaimed from the compound claims of the present invention. 5,6-Diphenyl-2-pyrazinecarboxylic acid is disclosed in CH 458 361.

Co-pending application PCT/GB02/05742 discloses compounds of the general formula (I)



I

and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, in which

R^1 and R^2 independently represent:

a C_{1-6}alkyl group;

an (amino)C_{1-4}alkyl– group in which the amino is optionally substituted by one or more C_{1-3}alkyl groups;

an optionally substituted non-aromatic C_{3-15}carbocyclic group;

a (C_{3-12}cycloalkyl)C_{1-3}alkyl– group;

a group $-(CH_2)_r$(phenyl $)_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

1-adamantylmethyl;

a group – $(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-5}alkyl group, a C_{1-5}alkoxy group or halo;

or R^1 represents H and R^2 is as defined above;

or R^1 and R^2 together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

X is CO or SO_2;

Y is absent or represents NH optionally substitututed by a C_{1-3}alkyl group;

R^3 and R^4 independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one, two or three groups represented by Z;

Z represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di

C_{1-3}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl and acetyl; and

R^5 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, a hydroxyC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula $-CONHNR^aR^b$ wherein R^a and R^b are as previously defined for R^1 and R^2 respectively;

with the proviso that when R^1 and R^2 together with the nitrogen atom to which they are attached represent 4-methylpiperazin-1-yl or R^1 represents H and R^2 represents methyl or 1-benzylpiperidin-4-yl; X is CO; Y is absent and R^5 is H; then R^3 and R^4 do not both represent 4-methoxyphenyl; and their use in the treatment of obesity, psychiatric and neurological disorders.

Surprisingly a particular compound has advantageous properties and provides a selection invention from the above application.

Description of the invention

The invention relates to 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof.

"Pharmaceutically acceptable salts", where such salts are possible, include pharmaceutically acceptable acid and base addition salts. All tautomers, where possible, are included within the scope of the invention.

The compounds may be prepared as described in the Examples and by analogous methods.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient or a pharmaceutically acceptable addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and

patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof, are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, septic shock and diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea). The compounds are also potentially useful as agents in treatment of extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms. The compounds may also eliminate the increase in weight, which normally accompanies the cessation of smoking.

In another aspect the present invention provides 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof, as previously defined for use as a medicament.

In a further aspect the present invention provides the use of 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof, in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

The compounds of the present invention are particulary suitable for the treatment of obesity, e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of obesity such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and atherosclerosis. For example, a compound of the present invention may be used in combination with a compound that affects thermogenesis, lipolysis, fat absorption, satiety, or gut motility. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of obesity and its associated complications the metabolic syndrome and type 2 diabetes, these include biguanide drugs, insulin (synthetic insulin analogues) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors).

In another aspect of the invention, 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or a pharmaceutically acceptable salt thereof may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to

in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin.

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present invention also includes a compound of the present invention in combination with a bile acid binding resin.

The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor;

a cholesterol absorption antagonist;

a MTP (microsomal transfer protein) inhibitor ;

a nicotinic acid derivative, including slow release and combination products;

a phytosterol compound ;

probucol;

an anti-coagulant;

an omega-3 fatty acid ;

another anti-obesity compound;

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

an SSRI;

a serotonin antagonist;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of obesity and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof, in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof, in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:
a) 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof, in a first unit dosage form;
b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:
a) 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or

pharmaceutically acceptable salts thereof and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of obesity and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide or pharmaceutically acceptable salts thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatorheic hepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

Examples

Abbreviations

DCM - dichloromethane

DMF - dimethylformamide

DMAP - 4-dimethylaminopyridine

EDC - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

TEA – triethylamine

TFA – trifluoroacetic acid

DMSO-dimethyl sulfoxide

DEA - Diethylamine

PCC - Pyridinium chlorochromate

DCM - Dichloromethane

PyBOP - benzotriazol-1-yl-oxytri-pyrrolidinophosphonium hexafluorophosphate

HBTU - *O*-Benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium Hexafluorophosphate

DAST-(diethyl amino)sulphur trifluoride

DIEA - *N,N*-diisopropylethylamine

t	triplet
s	singlet
d	doublet
q	quartet
qvint	quintet
m	multiplet
br	broad
bs	broad singlet
dm	doublet of multiplet
bt	broad triplet
dd	doublet of doublet

General Experimental Procedures

Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass LCZ single quadrupole mass spectrometer both equipped with a pneumatically assisted electrospray interface (LC-MS). ^{1}H NMR measurements were performed on either a Varian Mercury 300 or a Varian Inova 500, operating at ^{1}H frequencies of 300 and 500 MHz respectively. Chemical shifts are given in ppm with $CDCl_3$ as internal standard. $CDCl_3$ is used as the solvent for NMR unless otherwise stated. Purification was performed on a semipreparative HPLC with a mass triggered fraction collector, Shimadzu QP 8000 single quadrupole mass spectrometer equipped with 19 x 100 mm C8 column. The mobile phase used was, if nothing else is stated, acetonitrile and buffer (0.1 M NH_4Ac:acetonitrile 95:5).

For isolation of isomers, a Kromasil CN E9344 (250 x 20 mm i.d.) column was used. Heptane:ethyl acetate:DEA 95:5:0.1 was used as mobile phase (1 ml/min). Fraction collection was guided using a UV-detector (330 nm).

Examples of the Invention

Example 1

a) 1,2-bis(4-chlorophenyl)-2-hydroxyethanone

To 4-chlorobenzaldehyde (140.6 g, 1 mol) in ethanol (130 ml) was added a solution of sodium cyanide (10.6 g, 0.216 mol) in water (105 ml). The mixture was heated at reflux for 2.5 h and then extracted with DCM. The organic phase was washed with sodium bisulfite solution and the solvent was evaporated in vacuo. The compound was isolated by crystallization from diethyl ether/heptane. 48 g, 34%.

^{1}H NMR (400 MHz) δ 7.82 (d, 2H), 7.38 (d, 2H), 7.30 (d, 2H), 7.24 (d, 2H), 5.87 (s, 1H), 4.47 (s, 1H).

MS *m/z* 279, 281 $(M-H)^-$.

b) 1,2-bis(4-chlorophenyl)ethane-1,2-dione

1,2-bis(4-chlorophenyl)-2-hydroxyethanone, (90 g, 0.320 mol) and nitric acid (170 ml) were heated at 100°C until the evolution of nitrogen oxides ceased after 4 hours. The reaction mixture was cooled, and water (250 ml) was carefully added. The crude product was filtered, washed several times with water and dried under reduced pressure to give a yellow solid (40.4 g, 45%).

^{1}H NMR (500 MHz) δ 7.94 (d, 4H), 7.53 (d, 4H).

c) 5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarbonitrile

1,2-bis(4-chlorophenyl)ethane-1,2-dione, (20 g, 71.65 mmol), diaminomaleonitrile (8.5 g, 78.82 mmol) and acetic acid (6 ml) in ethanol (140 ml) and water (93 ml) were heated at 75 °C overnight. The reaction mixture was cooled, and water was added. The precipitate was filtered and washed with ethanol and then ether. The crude product was dissolved in DCM and treated with activated charcoal, then filtered through celite. After evaporation, a solid was formed and recrystallized from DCM/ethanol to give a pale yellow solid (17.3 g, 69%).

^{1}H NMR (400 MHz) δ 7.49 (d, 4H), 7.38 (d, 4H).

d) 5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarboxylic acid

To 5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarbonitrile, (16.3 g, 46.28 mmol) and KOH (26 g, 463 mmol) in water (84 ml) was added hydrogen peroxide (35%, 19 ml) followed by a few drops of nonanol to reduce foaming. The reaction mixture was heated at reflux for 2h, cooled and washed once with diehtyl ether and acidified to pH 4 with 2M HCl. The precipitate was collected through a filter, washed with water and dried under reduced pressure to give the crude product. The crude product was convertd to dimethyl ester by refluxing with hydrogen chloride/methanol (100 ml) and purified by HPLC, giving 12.85 g of the methyl ester. The resulting methyl ester was treated with lithium hydroxide (2.95 g, 0.123 mmol) in acetonitrile (140 ml) and water (90 ml) at ambient temperature for 1.5 h. The acetonitrile was removed under reduced pressure and the aqueous solution was washed once with diethyl ether. Acidification with hydrochloric acid (2M) and filtration gave the title compound (11.8 g, 66% mmol) as a pale yellow solid.

^{1}H NMR (400 MHz) δ 7.51 (d, 4H), 7.41 (d, 4H). MS *m/z* 389, 391 $(M+H)^+$.

e) 2,3-bis(4-chlorophenyl)furo[3,4-*b*]pyrazine-5,7-dione

5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarboxylic acid (6.7 g, 17.30 mmol) and acetyl chloride (20 ml) were boiled under reflux overnight. The acetyl chloride was removed under reduced pressure to give the title compound (6.2 g, 97%) as a pale yellow solid.

^{1}H NMR (400 MHz) δ 7.51 (d, 4H), 7.41 (d, 4H).

f) 5,6-bis(4-chlorophenyl)-3-(piperidin-1-ylcarbonyl)pyrazine-2-carboxylic acid

Piperidine (57 mg, 0.67 mmol) was mixed with 2,3-bis(4-chlorophenyl)furo[3,4-*b*]pyrazine-5,7-dione (238 mg, 0.64 mmol) in acetonitrile (10 ml). After 10 minutes the solvent was removed in vacuo to give the title compound (262 mg, 90%).

^{1}H NMR (400 MHz) δ 7.48-7.38 (m, 4H), 7.37-7.28 (m, 4H), 3.86-3.76 (m, 2H), 3.35-3.23 (m, 2H), 1.83-1.65 (m, 4H), 1.64-1.53 (m, 2H).

MS *m/z* 456, 458 $(M+H)^+$, 454, 456 $(M-H)^-$.

This compound is believed to be a novel intermediate and is herein claimed as another aspect of the present invention.

g) 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-ylcarbonyl)pyrazine-2-carboxamide

Oxalyl chloride (1 ml), DMF (2 drops), and 5,6-bis(4-chlorophenyl)-3-(piperidin-1-ylcarbonyl)pyrazine-2-carboxylic acid, (246 mg, 0.54 mmol) were mixed in DCM (3 ml). After 30 minutes the solvent and excess oxalyl chloride was removed in vacuo with the aid of toluene. The residue was dissolved in toluene (15 ml) and piperidin-1-amine (135 mg, 1.35 mmol) was added. After 24 h the solution was diluted with toluene and washed with hydrochloric acid, sodium carbonate solution, and brine. Drying (magnesium sulfate) and evaporation of the solvent gave a residue that was purified by preparative HPLC to give the target compound.

^{1}H NMR (400 MHz) δ 8.29 (s, 1H), 7.45-7.40 (d, 2H), 7.40-7.33 (m, 4H), 7.32-7.27 (d, 2H), 3.84-3.76 (m, 2H), 3.34-3.27 (m, 2H), 2.90-2.81 (m, 4H), 1.81-1.51 (m, 10H), 1.50-1.39 (m, 2H).

MS *m/z* calcd for $[C_{28}H_{30}Cl_2N_5O_2]H^+$ 538.1777, found 538.1729 $(M+H)^+$

Pharmacological Activity

Compounds of the present invention are active against the receptor product of the CB1 gene. The affinity of the compounds of the invention for central cannabinoid receptors is demonstrable in methods described in Devane et al, Molecular Pharmacology, 1988, 34,605 or those described in WO01/70700 or EP 656354. Alternatively, the assay may be performed as follows.

10μg of membranes prepared from cells stably transfected with the CB1 gene were suspended in 200μl of 100mM NaCl, 5mM $MgCl_2$, 1mM EDTA, 50mM HEPES (pH 7.4), 1mM DTT, 0.1% BSA and 100μM GDP. To this was added an EC80 concentration of agonist (CP55940), the required concentration of test compound and 0.1μCi [^{35}S]-GTPγS. The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred on to GF/B filters using a cell harvester and washed with wash buffer (50mM Tris (pH 7.4), 5mM $MgCl_2$, 50mM NaCl). Filters were then covered with scintilant and counted for the amount of [^{35}S]-GTPγS retained by the filter.

Activity is measured in the absence of all ligands (minimum activity) or in the presence of an EC80 concentration of CP55940 (maximum activity). These activities are set as 0% and 100% activity respectively. At various concentrations of novel ligand, activity is calculated as a percentage of the maximum activity and plotted. The data are fitted using the equation y=A+((B-A)/1+((C/x) ÙD)) and the IC50 value determined as the concentration required to give half maximal inhibition of GTPγS binding under the conditions used.

The compounds of the present invention are active at the CB1 receptor (IC50 <1 micromolar). Most preferred compounds have IC50 <200 nanomolar. 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide and

pharmaceutically acceptable salts thereof are selected because of their superior potency *in vitro* and/or higher affinity, leading to better *in vivo* efficacy. The compounds also have a better selectivity profile, which is expected to improve *in vivo* safety.

In addition the compounds of the present invention may have improved DMPK (Drug Metabolism and Pharmacokinetic) properties, for example improved metabolic stability *in vitro* or bioavailability. The compounds also have an improved solubility and/or a promising toxicological profile.

Claims

1. 5,6-Bis(4-Chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-ylcarbonyl)pyrazine-2-carboxamide and/or pharmaceutically acceptable salts thereof.

2. 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide and/or pharmaceutically acceptable salts thereof for use as a medicament.

3. A pharmaceutical formulation comprising 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide and/or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable adjuvant, diluent or carrier.

4. Use of 5,6-bis(4-chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide and/or pharmaceutically acceptable salts thereof in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications.

5. A method of treating obesity, psychiatric disorders, psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, neurological disorders, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal system, and extended abuse, addiction and/or relapse indications, comprising administering a pharmacologically effective amount of 5,6-bis(4-

chlorophenyl)-*N*-piperidin-1-yl-3-(piperidin-1-yl-carbonyl)pyrazine-2-carboxamide and/or pharmaceutically acceptable salts thereof to a patient in need thereof.

6. A compound as defined in either claim 1 for use in the treatment of obesity.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000967

A. CLASSIFICATION OF SUBJECT MATTER
IPC7: C07D401/14, A61K31/497, A61P3/04, A61P25/00, A61P37/00, A61P09/00, A61P05/00, A61P11/00, A61P01/00 //C07D401/14, C07D241:24, C07D211:06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM ABS DATA, EPO-INTERNAL, WPI DATA, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03051851 A1 (ASTRAZENECA AB), 26 June 2003 (26.06.2003) --	1-6
P,X	WO 03051850 A1 (ASTRAZENECA AB), 26 June 2003 (26.06.2003) --	1-6
A	WO 9202513 A1 (FUJISAWA PHARMACEUTICAL CO., LTD.), 20 February 1992 (20.02.1992) --	1-6

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 October 2004	20 -10- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer PER RENSTRÖM/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000967

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Akihiro Ohta, Hiromitsu Takahashi, Naoomi Miyata, Hiroyuki Hirono, Toyotaka Nishio, Etsuo Uchino, Kenji Yamada, Yutaka Aoyagi,, Yasushi Suwabe, Masayuki Fujitake, Takahiro Suzuki, Kazuo Okamoto,"Anti-Platelet Aggregation Activity of Some Pyrazines", Biol. Pharm. Bull. (1997), 20(10): 1076-1081	1-6
A	WO 0170700 A1 (SOLAVY PHARMACEUTICALS B.V.), 27 Sept 2001 (27.09.2001)	1-6
A	EP 656354 A1 (SANOFI), 7 June 1995 (07.06.1995)	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000967

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 5
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box II.1

Claim 5 relates to methods of treatment of the human or animal body by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/09/2004

International application No.
PCT/SE 2004/000967

WO	03051851	A1	26/06/2003	CA	2469786 A	26/06/2003
				SE	0104330 D	00/00/0000
WO	03051850	A1	26/06/2003	SE	0104332 D	00/00/0000
WO	9202513	A1	20/02/1992	GB	9017183 D	00/00/0000
				JP	6501926 T	03/03/1994
				GB	9020345 D	00/00/0000
WO	0170700	A1	27/09/2001	AU	4250101 A	03/10/2001
				BR	0109457 A	03/06/2003
				CA	2401832 A	27/09/2001
				CN	1419546 T	21/05/2003
				EP	1268435 A	02/01/2003
				HU	0204519 A	28/05/2003
				IL	151452 D	00/00/0000
				JP	2004500401 T	08/01/2004
				NO	20024531 A	19/11/2002
				SK	13522002 A	04/03/2003
				US	6476060 B	05/11/2002
				US	20010053788 A	20/12/2001
				ZA	200207303 A	11/12/2003
EP	656354	A1	07/06/1995	NONE		